REMARKS

Reconsideration and withdraw of the objections to and/or rejections of the application are respectfully requested in view of the amendments, remarks and amendments herewith.

Status of the Claims and Formal Matters

Claims 1-7 and 16-29 are under examination in this application. New claims 16-29 have been added.

No new matter is added. Support for the new claims is found throughout the specification.

Applicants acknowledge withdraw of previous rejections under 35 U.S.C. § 112, first paragraph and 35 U.S.C. § 103, in view of Vacanti et al. (1988) and U.S. 5,759,830, in view of Locopo et al. (1998) and Streit et al. (1999). The Examiner is thanked for consideration of arguments presented in the June 4, 2002 Office Action Response and actions taken accordingly.

It is submitted that the claims, herewith and as originally presented, are patentably distinct over the prior art cited by the Examiner, and that these claims were in full compliance with the requirements of 35 U.S.C. §112. The amendments of and additions to the claims, as presented herein, are not made for purposes of patentability within the meaning of 35 U.S.C. §§§§ 101, 102, 103 or 112. Rather, these amendments and additions are made simply for clarification and to round out the scope of protection to which Applicants are entitled. Furthermore, it is explicitly stated that the herewith amendments should not give rise to any estoppel, as the herewith amendments are not narrowing amendments.

Oath/Declaration

A new Declaration, identifying the present application by serial number and filing date and claiming priority to U.S. applications Serial Nos. 09/536,087, 60/178,842 and 09/77,339 is attached. Reconsideration and withdrawal of the objection to the oath/declaration are requested.

Specification

The specification has been amended to indicate that the instant application is a continuation-in-part of U.S. applications Serial Nos. 09/536,087 and 09/770,339, both pending. Reconsideration and withdrawal of the rejection of the specification are requested.

To the extent a Petition is needed for this amendment, this paper is to serve as such, with it explicitly stated that any failure to claim or state continuing status previously was inadvertent,

and any fee for the petition, if needed, be charged to Deposit Account No. 50-0320 (with it noted that this application qualifies for small entity status).

Priority Claim

The objection to the domestic priority claim under 35 U.S.C. § 119(e) based on provisional application No. 60/127,221 ("the '221 application") is respectfully traversed. The '221 application discloses a method of treating a subject with a disorder characterized by unwanted cell proliferation by increasing expression of TSP-2. As disclosed on pages 5 and 18 of the '221 application, this can be accomplished by introducing into the subject a genetically modified cell that expresses the molecule. The '221 application states on page 39 that the gene therapy construct "can comprise a slow release matrix in which the gene delivery vehicle is imbedded." Such a matrix is encompassed by that of the instant application, which states on page 11 "[b]ioactive materials may also be incorporated into the device or a sustained release matrix within the device to promote cell viability or proliferation." Applicants request that the objection to the claim of priority under 35 U.S.C. § 112(e) be reconsidered and withdrawn.

THE REJECTION UNDER 35 U.S.C. §112, 1ST PARAGRAPH, IS OVERCOME

Claims 1-7 were rejected under 35 U.S.C. §112, first paragraph, as allegedly lacking enablement. The rejection is traversed.

The Office Action asserts that the specification does not teach that any anti-angiogenic molecule other than thrombospondin-2 (TSP-2) may be used in the methods of the invention. The use of TSP-2 is exemplified, however, it is explicitly stated that other anti-angiogenic molecules can be used at several places in the application. For example, on page 7, line 15, the application reads, "Any biologically active anti-angiogenic molecule which has been cloned or for which a cellular source is available can be used."

According to the Court of Appeals for the Federal Circuit in the case of *In re Wands*, 8 U.S.P.Q.2d 1400 (Fed. Cir. 1988):

> Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is undue, not experimentation. The determination of what constitutes undue experimentation in a given case requires the application of standard of reasonableness, having due regard for the nature of the invention and the state of the art. The

> test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed ... [Citations omitted].

Id. at 1404.

Against this background, determining whether undue experimentation is required to practice a claimed invention turns on weighing many factors summarized in *In re Wands* (*Id.*). For example, (1) the quantity of experimentation necessary; (2) the amount of direction or guidance presented; (3) the presence or absence of working examples of the invention; (4) the nature of the invention; (5) the state of the prior art; (6) the relative skill of those in the art; (7) the predictability or unpredictability of the art; and (8) the breadth of the claims.

Applying *Wands* to the instant facts, enablement is shown to exist. The amount of direction or guidance presented is high; working examples are present; the prior art is replete with references characterizing the structure and activity of anti-angiogenic molecules; the relative skill of those in the art is high; and the predictability of the art is also high.

It would appear that the Examiner's rejection is based on the fact that the Examples exemplify data obtained using TSP-2 and not other anti-angiogenic molecules described in the specification, such as TSP-1, thrombomodulin, angiostatin and endostatin.[1] As stated in MPEP 2164.02, "[t]he presence of only one working example should never be the sole reason for rejecting claims as being broader than the enabling disclosure... To make a valid rejection, one must evaluate all the facts and evidence and state why one would not expect to be able to extrapolate that one example across the entire scope of the claims." MPEP 2164.02 goes on to say, "[p]roof of enablement will be required for other members of the claimed genus only where adequate reasons are advanced by the examiner to establish that a person skilled in the art could not use the genus as a whole without undue experimentation." Such evidence has not been provided here.

In fact, there is no evidence that the skilled artisan would have to practice undue experimentation. Any molecule known to inhibit angiogenesis could be used in the present invention to treat excess tissue proliferation, which is dependent upon angiogenesis. Therefore,

[1] On page 4, the Office Action alleges that "[t]he specification discloses a method of treatment comprising implanting a cell-matrix structure with attached cells, which express a gene encoding TSP-2, but not thrombomodulin or any other molecule. There is no teaching or exemplification in the specification indicating that thrombomodulin or any molecule other than TSP-2 may be used in the method as claimed."

the assertion that the specification only enables claims to TSP-2 is outweighed by the arguments and evidence presented herein.

As stated above, the application states that any anti-angiogenic molecule can be used. It goes on to name angiogenesis inhibitors such as TSP-1, angiostatin and endostatin, and gives references that characterize these molecules. (See page 7, paragraph beginning at line 28.) Further, as the original claims are considered part of the disclosure (MPEP 608.01(l)), thrombomodulin is disclosed as well.

Knowledge of the structure and function of anti-angiogenesis molecules is a well-developed art, as is evidenced by the attached documents, which demonstrate the state of the art at the time the instant application was filed. For example, Hagedorn and Bikfalvi (2000) Crit. Rev. Oncol. Hematol. 34(2):89-110 profile the large number of diseases that can be treated by various anti-angiogenic compounds such as angiostatin, endostatin and thrombospondins. They discuss several inhibitors of angiogenesis and demonstrate that many of these molecules are well-characterized. *See*, for example, page 97 of Hagedorn and Bikfalvi (2000). Likewise, Kirsch et al. (2001) Onkologie 24:423-430 also describe the anti-angiogenic effects of these molecules. Cherrington *et al.* (2000) Adv. Cancer Res. 79:1-38 highlight the therapeutic potential of anti-angiogenic factors in their discussion of such molecules that are already in clinical trials. Carpizo and Iruela-Arispe (2000) Cancer Metastasis Rev. 19(1-2):159-65 echo Cherrington *et al.*, and elaborate specifically on two families of anti-angiogenic proteins, thrombospondins and metallospondins. *See*, for example, Carpizo and Iruela-Arispe (2000), page 159, (stating "[t]he acknowledgement that TSP1 can function as an endogenous inhibitor of angiogenesis is now 10 years old."). Importantly, they discuss the conserved anti-angiogenic functional domain. This underscores the similarity of these types of molecules, and further disputes the assertion by the Examiner that the use of molecules other than TSP-2 would require undue experimentation by the skilled artisan.

Thus, proper balancing of the relevant factors in *Wands* shows that the Examiner's rejection is outweighed as based on a single factor (exemplification) that is not lacking or deficient in the instant application. The presence of working examples depicting TSP-2, taken in combination with the literature discussed above, is more than sufficient to establish that a person skilled in the art could use the anti-angiogeneic genus as a whole without undue experimentation. All criteria for exemplification are fulfilled in the instant application.

The Examiner's attention is respectfully directed to new claims 16-23, reciting TSP-2. These claims are fully responsive to the Examiner's rejections—which are traversed—and should be immediately allowable.

CONCLUSION

In view of the amendments and remarks herewith, the application is in condition for allowance. Favorable reconsideration of the application and prompt issuance of a Notice of Allowance are earnestly solicited. No fee is believed to be due for entry and consideration of this paper, however, any fee occasioned by this paper may be charged, or overpayment credited to, Deposit Account No. 50-0320.

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Specification

On page 1, line 5:

This application is a continuation-in-part of [claims priority to] U.S.S.N. 09/536,087, filed March 24, 2000, which claims priority to U.S.S.N. 60/127,221, filed March 31, 1999. [, and to] This application is also a continuation-in-part of U.S.S.N. 09/770,339, filed January 26, 2001, which claims priority to U.S.S.N. 60/178,842, filed January 27, 2000.

In the Claims

1. (Amended) A method for treating a disorder characterized by excessive proliferation of tissue comprising implanting a cell-matrix structure [comprising a matrix having attached thereto an effective amount of cells stably expressing a gene encoding an antiangiogenic molecule in an amount effective to inhibit or regress the excessive tissue proliferation] in an amount sufficient to stop or regress the excessive tissue proliferation, wherein said cell-matrix structure comprises a matrix having attached thereto cells stably expressing a gene encoding an anti-angiogenic molecule [wherein the cells are either genetically engineered to produce the anti-angiogenic molecule or of a different cell type than the tissue that has proliferated excessively and naturally produce the anti-angiogenic molecule].

5. (Amended) The method of claim 1 [5] wherein the cells are genetically engineered to produce the anti-angiogenic molecule.

6. (Amended) The method of claim 1 [6] wherein the anti-angiogenic molecule is thrombomodulin.